Articles

Primary Mediastinal Malignancies: Findings in 219 Patients

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The purpose of this study was to determine the demographics, histology, methods of treatment, and survival in primary mediastinal malignancies. We did a retrospective review of the statewide New Mexico Tumor Registry for all malignant tumors treated between January 1, 1973 and December 31, 1995. Benign tumors and cysts of the mediastinum were excluded. Two hundred nineteen patients were identified from a total of 110,284 patients with primary malignancies: 55% of tumors were lymphomas, 16% malignant germ cell tumors, 14% malignant thymomas, 5% sarcomas, 3% malignant neurogenic tumors, and 7% other tumors. There were significant differences in gender between histologies ($P < 0.001$). Ninety-four percent of germ cell tumors occurred in males, 66% of neurogenic tumors were in females; other tumors occurred in males in 58% of cases. There were also significant differences in ages by histology ($P < 0.001$). Neurogenic tumors were most common in the first decade, lymphomas and germ cell tumors in the second to fourth decades, and lymphomas and thymomas in patients in their fifth decades and beyond. Stage at presentation ($P = 0.001$) and treatment ($P < 0.001$) also differed significantly between histologic groups. Five-year survival was 54% for lymphomas, 51% for malignant germ cell tumors, 49% for malignant thymomas, 33% for sarcomas, 56% for neurogenic tumors, and 51% overall. These survival rates were not statistically different ($P > 0.50$). Lymphomas, malignant germ cell tumors, and thymomas were the most frequently encountered malignant primary mediastinal neoplasms in this contemporary series of patients. Demographics, stage at presentation, and treatment modality varied significantly by histology. Despite these differences, overall five-year survival was not statistically different.

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Mediastinal malignancies are uncommon. Consequently, contemporary series using modern diagnostic and therapeutic modalities are rare. We reviewed the statewide New Mexico Tumor Registry for all cases of mediastinal malignancy diagnosed during the years 1973 through 1995.

Materials and Methods

The New Mexico Tumor Registry National Cancer Institute Surveillance, Epidemiology, and End Results program (SEER) statewide data base was used to abstract all cases of malignant, primary tumors diagnosed between January 1, 1973 and December 31, 1995 within the state of New Mexico. This registry contains all primary tumors diagnosed within the state and is not selected by treatment center, treatment type, physician, or referral pattern. From these cases, some were selected for further analysis using identifiers for primary sites of origin from thymus; anterior, posterior, or not otherwise specified mediastinum; intrathoracic lymph nodes; heart; peripheral nerves and autonomic nervous system of the thorax. Primary tumors of the thyroid, parathyroid, airway, esophagus, and lung were excluded. Statistical analysis was performed using Fisher exact test for binary variables, Wilcoxon rank sum test for non-normally distributed data, life table analysis for survival data, and Kruskal-Wallis analysis for age distributions.

Results

Two hundred nineteen patients with primary mediastinal malignancies were identified from a population of 110,284 patients with primary malignant tumors.

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TABLE 1.—*Histologic Classification of Primary Mediastinal Malignancies*

Histology	No. Pts.	%
Lymphoproliferative	121	55
Hodgkin's	42	
Non-Hodgkin's	79	
Germ cell	34	16
Seminoma	17	
Nonseminoma	17	
Thymoma	31	14
Sarcoma	12	5
Neurogenic	6	3
Neuroblastoma	5	
Ganglioneuroblastoma	1	
Other	15	7
Total	219	100

TABLE 3.—*Treatment Modalities for Primary Mediastinal Malignancies**

Histology	Surgery (%)	MED (%)	XRT (%)	No Treatment
Lymphoproliferative	16 (15)	85 (77)	58 (53)	11
Hodgkin's	6	27	29	1
Non-Hodgkin's	10	58	29	10
Germ cell	17 (50)	26 (76)	15 (44)	0
Seminoma	6	12	7	0
Nonseminoma	11	14	8	0
Thymoma	19 (63)	13 (43)	21 (70)	1
Sarcoma	8 (89)	6 (67)	5 (56)	3
Neurogenic	5 (100)	0 (0)	1 (20)	1
Other	8 (72)	2 (18)	10 (91)	4
Total	73 (37)	132 (66)	110 (55)	20

*Percentages are treated patients receiving modality as part or all of treatment.

Sixty-three percent were male (138/219) and 37% were female (81/219). Median age was 47 years. Sixty-eight percent (149/219) were non-Hispanic whites, 27% (60/219) were Hispanic whites, 3% (6/219) were Native American, and less than 2% were black or of other ethnicity. Histologic confirmation was present in 95% of patients (209/219).

Table 1 shows tumor histology. A total of 51 histologic subtypes were diagnosed. Lymphoproliferative malignancies were most common and present in 55% of patients. Other tumor classes, listed in decreasing order of frequency, were malignant germ cell tumor in 16% of patients, malignant thymoma in 14%, sarcoma in 5%, neurogenic malignancy in 3%, and other malignancies in 7%.

Table 2 presents staging. Localized disease, defined as a tumor confined entirely to the organ of origin, was present in 40% of patients; regional disease, defined as disease extending directly into surrounding organs or tissues and/or involving regional lymph nodes, was present in 27%; and distant disease, defined as tumor spread to remote areas of the body, was present in 29%. Staging was unknown in 5% of patients. In tumors other than lymphoma, staging was localized in 28% (27/98), regional in 38% (37/98), remote in 29% (28/98), and unknown in 6% (6/98).

Table 3 lists treatments. Medical therapy (MED) was used most commonly and was part or all of treatment in 66% of treated patients. Medical therapy consisted primarily of chemotherapy, but by definition within the registry, also included any hormonal or immunotherapy. Radiation therapy (XRT) was part or all of treatment in 55%, and surgery was part or all of treatment in 37% of the total group and in 63% (57/90) of treated patients without lymphoproliferative malignancies.

Table 4 lists survivals. Five-year survival was 51% for the entire group. Survival was 54% for lymphoma, 51% for malignant germ cell tumors, 49% for malignant thymoma, 33% for sarcoma, and 56% for neurogenic tumors.

Lymphoproliferative malignancies were subtyped as Hodgkin's lymphomas in 35% and non-Hodgkin's

TABLE 2.—*Staging of Primary Mediastinal Malignancies*

Histology	Local (%)	Region. (%)	Distant (%)	Unkn. (%)
Lymphoproliferative	60 (50)	22 (18)	35 (29)	4 (3)
Hodgkin's	20	7	14	1
Non-Hodgkin's	40	15	21	3
Germ cell	7 (21)	13 (38)	12 (35)	2 (6)
Seminoma	4	7	6	0
Nonseminoma	3	6	6	2
Thymoma	5 (16)	15 (48)	9 (29)	2 (7)
Sarcoma	7 (58)	1 (8)	4 (33)	0 (0)
Neurogenic	3 (50)	2 (33)	1 (17)	0 (0)
Other	5	6	2	2
Total	87 (40)	59 (27)	63 (29)	10 (5)

TABLE 4.—*Five-Year Survival Percentages by Histology of Primary Mediastinal Malignancies*

Histology	Localized	Regional	Distant	Overall
Lymphoproliferative	55	64	43	54
Hodgkin's	85	78	62	77
Non-Hodgkin's	39	59	30	43
Germ cell	37	53	48	51
Seminoma	36	86	46	62
Nonseminoma	33	17	50	40
Thymoma	100	62	0	49
Sarcoma	57	0	0	33
Neurogenic	67	0	0	56
Total	57	55	35	51

lymphomas in 65% (Table 1). The most common lymphomas were nodular sclerosing Hodgkin's disease in 26% (32/121) and large-cell diffuse malignant lymphoma in 26% (32/121). Fifty-seven percent (69/121) of patients were male and 43% (52/121) female. There was no significant difference in gender distribution between Hodgkin's and non-Hodgkin's lymphomas (22/42 vs 47/79 males, $P > 0.5$). The median age was 45 (range 2–96) years for all lymphomas; the median age for Hodgkin's was significantly younger than the median age of non-Hodgkin's (28 Hodgkin's, range 11–71; 54 non-Hodgkin's, range 2–96; $P < 0.001$).

Lymphomas were staged as localized in 50% of patients, regional in 18%, remote in 29%, and unknown in 3% (Table 2). In treated patients, MED was part or all of treatment in 77% of patients (27/41 Hodgkin's, 58/69 non-Hodgkin's, $P = 0.04$); XRT was part or all of treatment in 53% of patients (29/41 Hodgkin's, 29/69 non-Hodgkin's, $P = 0.001$); and surgery was part or all of treatment in 15% of patients (6/41 Hodgkin's, 10/69 non-Hodgkin's, $P > 0.5$) (Table 3).

The five-year survival for patients with lymphoma was 54% (Table 4). Five-year survival for Hodgkin's disease was 77% and for non-Hodgkin's lymphoma was 43% ($P < 0.001$). Five-year survival of localized Hodgkin's disease was 85% compared to 39% for non-Hodgkin's lymphoma ($P = 0.001$).

Malignant germ cell tumors were subtyped as seminomas in 50% and nonseminomas in 50% (Table 1). The most common nonseminomatous tumor was malignant, mixed germ-cell tumor in 35% (6/17). Ninety-four percent of patients were male (17/17 seminoma, 15/17 nonseminoma, $P > 0.5$). Median age for the entire group was 27 years (28 seminoma, range 19–56; 26 nonseminoma, range 4–56; $P > 0.5$).

Germ cell tumors were localized in 21%, regional in 38%, remote in 35%, and unknown in 6% (Table 2). In treated patients, MED was part or all of treatment in 76% of patients (12/17 seminoma, 14/17 nonseminoma, $P = 0.21$); surgery was part or all of treatment in 50% of patients (6/17 seminoma, 11/17 nonseminoma, $P = 0.48$); and XRT was part or all of treatment in 44% of patients (7/17 seminoma, 8/17 nonseminoma, $P = 0.48$) (Table 3). The overall five-year survival of all malignant germ cell tumors was 51% (62% seminoma vs 40% nonseminoma, $P = 0.08$) (Table 4).

Malignant thymomas occurred in 14% of patients (Table 1). Fifty-eight percent (18/31) were male. Median age was 60 years (range 28–82). Sixteen percent were localized, 48% were regional, 29% were remote, and 7% were unknown (Table 2). In treated patients XRT was part or all of treatment in 70%, surgery was part or all of treatment in 63% patients, and MED was part or all of treatment in 43% (Table 3). The overall five-year survival of thymoma was 49% (Table 4). All patients with localized disease (5/5), and no patient with distant disease (0/9) were alive at five years ($P < 0.001$).

Sarcomas were present in 5% patients (Table 1). Fifty-eight percent (7/12) were male. Median age was 55 years (range 11–77). Fifty-eight percent were localized, 8% were regional, and 33% were remote (Table 2). In treated patients, surgery was part or all of treatment in 89% of patients, MED was part or all of treatment in 67% of patients, and XRT was part or all of treatment in 56% of patients (Table 3). Five-year survival was 33% (Table 4). No patient with regional or distant disease was alive at five years ($P = 0.08$).

Neurogenic tumors were present in only 3% of patients (Table 1). Neuroblastoma was present in 83% and ganglioneuroblastoma in 17%. Thirty-three percent (2/6) were male. Median age was less than 1 year (range 0–55). Fifty percent were localized, 33% regional, and 17% remote (Table 2). In treated patients surgery was part or all of treatment in 100% of patients, XRT was part or all of treatment in 20% of patients, and MED was not used in any patient (Table 3). Five-year survival was 56%. No patient with regional or distant disease was alive at five years ($P = 0.40$) (Table 4).

Other tumors were present in 7% of patients (Table 1). These consisted of malignant neoplasms not otherwise specified in 53% (8/15); mesothelioma and carcinoid tumor, each in 13% (2/15); and squamous carcinoma, carcinoma not otherwise specified, and malignant small cell tumor, each in 7% (1/12). None of these tumors were felt to represent metastatic disease.

Table 5 shows comparisons within the entire series between histologic types. There were significant differences in age and gender ($P < 0.001$), stage at presentation ($P = 0.001$), and in treatment with either MED or surgery ($P < 0.001$). Despite these differences, overall five-year survivals were not statistically different.

Discussion

Primary tumors and cysts of the mediastinum are uncommon: they represent only 1/1076 to 1/3400 admissions to tertiary care medical centers and approximately 3% of tumors within the chest.[1–4] In collected series of primary mediastinal tumors and cysts, 25% to 49% of these lesions are malignant.[1,2,4–13] This group of 219 patients, 0.2% of patients within our registry, represents a large series containing exclusively malignant primary mediastinal neoplasms.

The reported frequency of histologies depends upon the inclusion criteria of the series. Treatment or age selection, inclusion of benign tumors and cysts, and classification by anatomic location, tissue of origin, or pathologic diagnosis will affect results. Our series includes all patients with malignancies diagnosed within New Mexico between 1973 and 1995. Cases were not selected using any of these factors.

The gender distribution was relatively constant with two notable exceptions. Germ cell tumors occurred almost exclusively in males; only 6% of germ cell tumors, and none of the seminomas, developed in females. In contrast, 66% of neurogenic tumors occurred in females. Otherwise, 58% of lymphoma, thymoma, and sarcoma patients were male.

TABLE 5.—*Statistical Comparison Between Histologies (%)*

	Lymphoma	Germ Cell	Thymoma	Sarcoma	Neurogenic	P Value
Median age	45	27	60	55	1	<.001
Gender						<.001
Male	69 (57)	32 (94)	18 (58)	7 (58)	2 (33)	
Female	53 (43)	2 (6)	13 (42)	5 (42)	4 (67)	
Stage						.001
Localized	60 (50)	7 (21)	5 (16)	7 (58)	3 (50)	
Regional	22 (18)	13 (38)	15 (48)	1 (8)	2 (33)	
Distant	35 (29)	12 (35)	9 (29)	4 (33)	1 (17)	
Treatment						
Radiation	58 (53)	15 (44)	21 (70)	5 (56)	1 (20)	.15
Chemotherapy	85 (77)	26 (76)	13 (43)	6 (67)	0 (0)	<.001
Surgery	16 (15)	17 (50)	19 (63)	8 (89)	5 (100)	<.001
Survival						
Overall	(54)	(51)	(49)	(33)	(56)	>.50
Localized	(55)	(37)	(100)	(57)	(67)	.33
Regional	(64)	(53)	(62)	(0)	(0)	.40
Distant	(43)	(48)	(0)	(0)	(0)	.02
Total	121	34	31	12	6	

Histology varied notably by age (Figure 1). In the first decade, neurogenic tumors were most common. From the second to fourth decades, lymphoma and germ cell tumors predominated. After the fifth decade, lymphomas and thymomas were most common. Unlike the other tumors, sarcomas were evenly distributed in frequency over the entire age spectrum.

The most common tumor in our series was lymphoma. Other studies have variably reported lymphoma, germ cell tumors, thymoma, and primary mediastinal carcinomas to be the most common malignant primary mediastinal tumors.[1,2,4–8,12,14] Davis et al reported a series containing 166 malignant mediastinal tumors, of which lymphoma was most common and found in 37%.[8] Azarow et al reported the Walter Reed experience: lymphoma was the most common malignancy present in 45% of their 101 recent cases.[6] Cohen and co-workers reported an earlier Walter Reed series of 84 patients with malignant tumors: lymphoma was most common, present in 43% of patients.[7] Ovrum and Birkeland reported 34 malignant lesions of which lymphoma was most frequent and present in 32% of cases.[12] Heimburger et al also reported lymphoma to be the most common malignant histology present in 24% of their 37 cases.[1] Other series of primary mediastinal tumors report lymphoma to be present in 15% to 36% of malignant lesions.[2,4,5,9,11,14,15]

We found Hodgkin's disease in one third of lymphomas and non-Hodgkin's lymphoma in the remainder. Hodgkin's disease, usually nodular sclerosing, has been reported previously in 15% to 86% of mediastinal lymphomas.[4,5,8] Our most common subtypes were nodular sclerosing Hodgkin's and large-cell diffuse malignant lymphoma, each in 26%. Others have also found nodular sclerosing Hodgkin's or large-cell diffuse malignant lymphomas to be the most common subtypes of primary mediastinal lymphomas.[9,10,15,16] Our patients with Hodgkin's disease were significantly younger at presentation, treated more commonly with XRT and less often with MED, and had significantly better five-year survivals than patients with non-Hodgkin's lymphomas.

Mediastinal germ-cell tumors arise from malignant transformation of mediastinal primordial germinal elements. Only 1% to 3% of germ cell tumors occur within the mediastinum; 42% percent to 50% of these tumors are malignant.[3,6,8,–10,13] We found malignant germ cell tumors in 16% of our patients with malignant mediastinal tumors. Wongsangiem reported germ cell tumors in 47% of 62 patients with primary mediastinal malignancy.[4] Adkins and colleagues noted germ cell tumors in 29% of 38 malignant lesions.[5] Other studies have reported germ cell tumors to represent 3% to 14% of primary malignant mediastinal lesions.[1,2,6–9,11–14]

Seminoma is the most common malignant germ cell tumor of the mediastinum and has been reported to occur in 21% to 50% of malignant mediastinal germ cell tumors.[4,5,7,–10,13] We found seminoma in 50% of our patients. Despite all seminoma patients being male, there were no statistical differences between genders of seminomas and nonseminomas. Staging and treatment were also similar, but the five-year survival of 62% for seminomas was better than the 40% for nonseminomas. Other studies have reported overall five-year survivals of 45% for malignant germ cell tumors and 58% to 82% for seminomas.[3,5,8,13]

Malignant thymoma occurred in 14% of our patients. Thymoma was reported by Conkle and Adkins to be present in 26% of 43 patients with malignant lesions.[14] Rubush et al found thymoma in 59% of 61 patients

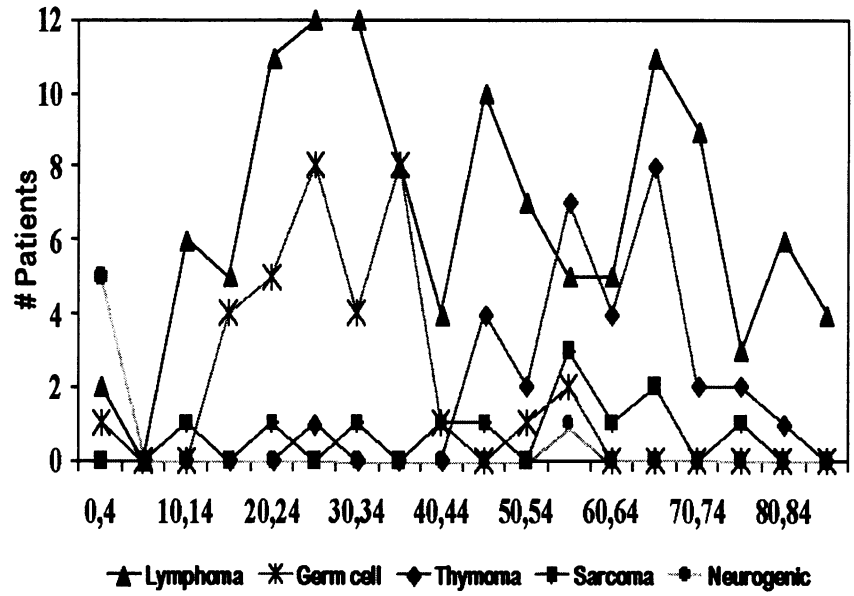

Figure 1.—Frequency of histologic types by age.

reported.[2] Nandi et al reported thymoma in 20% of 26 malignant tumors.[11] Others studies have reported malignant thymomas to represent 11% to 31% of primary malignant mediastinal masses.[1,4–8,12]

Thymomas are classified as malignant when the tumor invades into or beyond the capsule: This is reported in 39% to 46% of cases.[4,8,13] Because no evidence shows intrinsic differences between benign and malignant thymoma, abandoning this classification and considering all thymomas malignant has been recommended.[3,13] Noninvasive thymomas have been shown to have better survival than invasive thymomas. Only invasive thymomas are entered into the SEER registry, resulting in lower total numbers, lower resectability rates, and lower survivals than other reports in the literature. Surgical resection of thymomas has been performed in 82% to 100% of selected cases in previous reports, but only two thirds of our patients received surgery.[4,9,14] We found localized invasive thymoma had a significantly better survival rate than higher-stage invasive thymoma. Inclusion of only higher-stage thymomas resulted in a lower overall survival of 49% at five years than the 65% to 79% previously reported.[5,13,17–19]

We found sarcoma in 5% of our cases. Other studies have reported sarcomas in 2% to 8% of malignant primary mediastinal tumors.[1,2,4,7,8,10–14] Surgery was the primary treatment in 89% of treated patients. Five-year survival was significantly better for patients with localized tumors than for those with higher-stage sarcoma.

Neurogenic tumors are reported to be the most common primary mediastinal tumor in children; rates vary in adult series.[3,6,10,13] Six percent to 28% of these lesions are malignant overall.[8–10] We found malignant neurogenic tumors in 3% of our series. Other studies have reported neurogenic tumors in 2% to 21% of primary mediastinal malignancies.[1–8,10–14] Almost all tumors were neuroblastomas occurring in infants. Surgery was used in all treated patients. Overall five-year survival for our series was 56%, and only patients with localized disease survived.

Seven percent of patients had other, uncommon primary mediastinal malignancies. Others have reported primary carcinoma of the mediastinum in 7% to 30% of tumors.[1,5,7,10,12] Primary carcinoma of the mediastinum is poorly defined, however, and some cases may represent metastatic disease from unknown primaries. Many of these tumors in older series were misdiagnosed prior to the advent of modern pathologic diagnostic techniques.[5]

The prevalence of tumors in our series varied from some previously published reports. The rates of traditionally nonsurgical tumors such as lymphoma and malignant germ cell tumors are higher, and the rates of traditionally surgical diseases such as thymoma and neurogenic tumors are lower. The large number of patients in our study, the modern period under examination, the exclusion of benign tumors and cysts, and the absence of selection bias suggests our results are representative of the actual distribution of malignant mediastinal tumors.

This study demonstrates significant differences in demographics, stage at presentation, and treatment between histologies in a contemporary group of patients with these unusual tumors. Despite these differences, survival rate between histologic groups are not statistically different. The low incidence of these tumors suggests future use of tumor registries, and multi-institutional approaches may improve our experience and understanding of these tumors. The relatively poor five-year survival rate suggest further advances in treatments are needed. Just as with other thoracic malignancies, treatments may take the form of multimodality approaches in the future.

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